Effect of Lenvatinib on a Patient with Medullary Thyroid Carcinoma Liver Metastasis Caused by Multiple Endocrine Neoplasia Type 2A

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A 61-year-old female was diagnosed with multiple endocrine neoplasia type 2A (MEN2A), caused by a heterozygous point mutation in the RET gene (TGC to TAC at codon 634) resulting in the substitution of cytosine with leucine (C634Y). The patient had pheochromocytoma (PCC) in the left adrenal gland and medullary thyroid carcinoma (MTC) with liver metastasis. Primary hyperparathyroidism (PHP) was not evident. Family history data suggested that the RET gene mutation was inherited from the father. The PCC was removed laparoscopically, but the MTC was observed conservatively for 7 years because the status of the MTC was compatible with T1N1M1 and stage IVC; therefore, it was not curable with surgery. The MTC liver metastasis increased in size. Lenvatinib, an oral multi-tyrosine kinase inhibitor, was administered until the patient had received a total dose of 1336mg, and then administration was stopped because of nausea. The reduction rate of the MTC liver metastasis was 31%, which was considered partial response. At this point, the patient was doing well, suggesting that lenvatinib was effective in treating the MTC liver metastasis and may be one of the treatment for advanced MTC caused by C634Y mutation in the RET gene.

Key words: MEN2A, RET, Medullary thyroid carcinoma, Lenvatinib

INTRODUCTION

Multiple endocrine neoplasia type 2A (MEN2A) is an autosomal-dominant syndrome of multiple endocrine neoplasms, including medullary thyroid carcinoma (MTC), pheochromocytoma (PCC), and primary hyperparathyroidism (PHP) due to parathyroid adenoma or hyperplasia. Germline mutations in the RET gene are well documented as genetic causes of MEN2A [1, 2]. Patients with MEN2A have highly specific missense mutations in the extracellular cysteine-rich domain of the receptor, mainly at codons 609, 611, 620, 630, and 634 in exons 10 and 11. All these mutantions result in the substitution of cysteine with another amino acid. Codon 634 mutantions are the most common mutations associated with MEN2A, accounting for 100% of affected patients [1, 2].

A prognosis of MTC is generally favorable if the disease is treated at an early stage, as the 10-year survival rate is 70%-80% [3]. However, 10-year survival rates are less than 50% in patients with distant metastasis [3]. External-beam radiation therapy is of limited use against advanced MTC, and conventional cytotoxic chemotherapy has not been proven to prolong survival [4].

The constitutively active mutants of the RET gene associated with MTC have been shown to be very sensitive to agents that inhibit wild-type RET tyrosine kinase, providing a strong rationale for targeting RET mutants in patients with MTC [5]. In addition, MTC is vascular and increased expression of vascular endothelial growth factor (VEGF), which is associated with increased tumor growth and invasiveness [6]. Inhibitors of RET and VEGF receptor (VEGFR), which are tyrosine kinases, may exhibit an antitumor activity against MTC [4].

Lenvatinib, an oral multi-tyrosine kinase inhibitor (TKI) that selectively and directly targets RET, VEGFR, fibroblast growth factor receptor (FGFR), platelete-derived growth factor receptor (PDGFR), KIT, and epidermal growth factor receptor, is approved for the treatment of progressive MTC in patients with distant metastasis [7, 8].

In this report, we describe a 61-year-old Japanese female with MTC, MTC liver metastasis, and PCC caused by MEN2A. After conservative observation for 7 years, lenvatinib was administered, producing clinical improvement.

CASE REPORT

A 61-year-old Japanese female was referred to our hospital because of elevated serum carcinoembryonic antigen (CEA) level. Her height was 153.1 cm and she weighed 57.5 kg. Her blood pressure was 115/74 mmHg, and she had a regular pulse rate of 78 beats/minute.

The pedigree of the patient's family is illustrated in Fig. 1. The patient's father had undergone thyroidectomy for the thyroid tumor and abdominal surgery to remove the abdominal tumor, but the pathological

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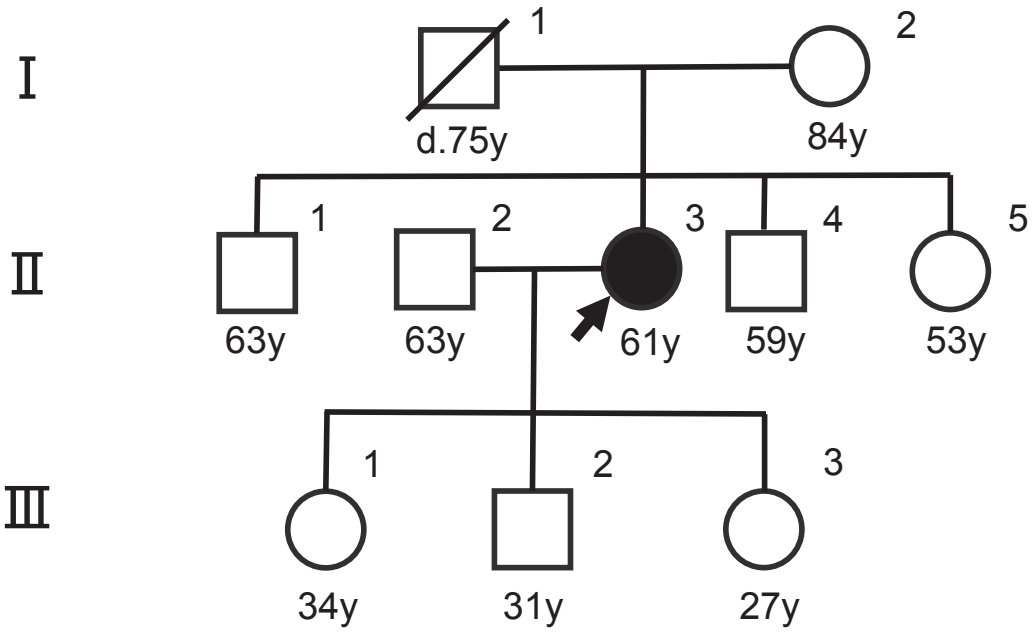

Fig. 1 Pedigree of the patient's family. The proband is indicated by the black arrow.

Table 1 Clinical laboratory findings

	Initial value	Reference range
WBC (/μl)	7500	4000–8000
RBC ($\times 10^4/\mu$l)	480	410–530
Hemoglobin (g/dl)	13.2	13.5–17.5
Hematocrit (%)	41.1	40.0–48.0
MCV (fl)	85.6	84.0–99.0
MCH (pg)	27.5	27.0–32.0
MCHC (%)	32.1	32.0–36.0
Platelets ($\times 10^4/\mu$l)	34.2	14.0–40.0
Albumin (g/dl)	4.1	3.9–4.8
AST (IU/l)	16	<30
ALT (IU/l)	16	<35
Creatinine (mg/dl)	0.5	0.5–0.8
Plasma glucose (mg/dl)	97	70–109
Total cholesterol (mg/dl)	205	140–220
Triglyceride (mg/dl)	172	50–150
Serum Na (mEq/l)	143	136–145
Serum K (mEq/l)	3.7	3.5–4.8
Serum Cl (mEq/l)	106	98–108
Serum Ca (mg/dl)	9.1	8.6–10.2
Serum P (mg/dl)	3.1	2.5–4.5

WBC, white blood cells; RBC, red blood cells; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration, AST, aspartate aminotransferase; ALT, alanine aminotransferase.

diagnoses were unknown. Her mother had no medical history. All the three siblings had no medical history. The patient had a son and two daughters who had no medical history.

Clinical laboratory findings are shown in Table 1 and 2. Serum CEA and calcitonin levels were 589.8 pg/ml and 22000 pg/ml, respectively. Ultrasonography of the neck revealed a right thyroid nodule with a maximum diameter of 9 mm and two enlarged lymph nodes in the right side of the neck, suggesting lymph node metastases. Aspiration cytology of the thyroid nodule confirmed MTC (Fig. 2).

Contrasted computed tomography (CT) revealed a tumor with a maximum diameter of 37 mm in the liver (Fig. 3A) and a left adrenal tumor (Fig. 3B). Iodine 131-labeled metaiodobenzylguanidine scintigraphy showed involvement of the left adrenal gland tumor and the liver tumor (Fig. 4). These findings suggested PCC of the left adrenal gland and MTC liver metastasis.

Hematoxylin and eosin staining of the liver needle biopsy specimen was shown (Fig. 5A). Immunohistochemical staining of the specimens was positive for CEA (Fig. 5B) and calcitonin (Fig. 5C).

Table 2 Endocrinological findings

	Value	Reference range
TSH (μIU/ml)	2.749	0.005–5.000
Free T4 (ng/dl)	0.98	0.90–1.70
Intact PTH (pg/ml)	26	10–65
Calcitonin (pg/ml)	22000	<3.91
CEA (pg/ml)	589.8	<5.0

TSH, thyroid stimulating hormone; T4, thyroxine; PTH, parathyroid hormone; CEA, carcinoembryonic antigen

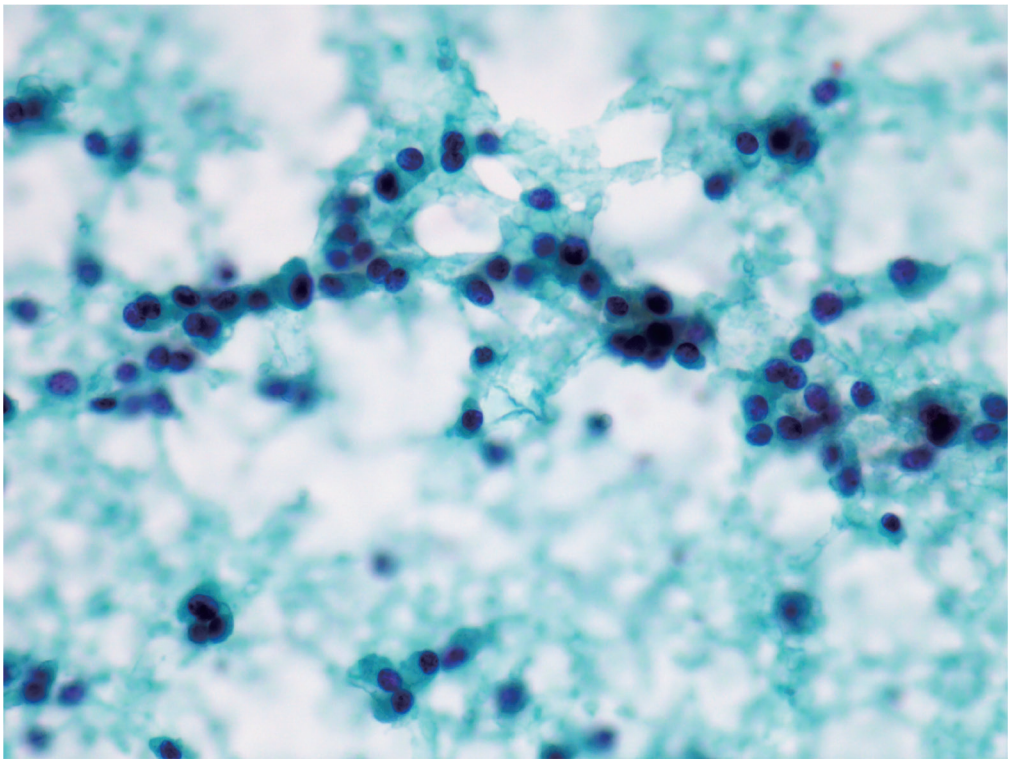

Fig. 2 Cytology showing cells are typically hypercellular with non-cohesive or loosely cohesive aggregations. The cells had varied shapes: polygonal, bipolar, or spindle shapes.

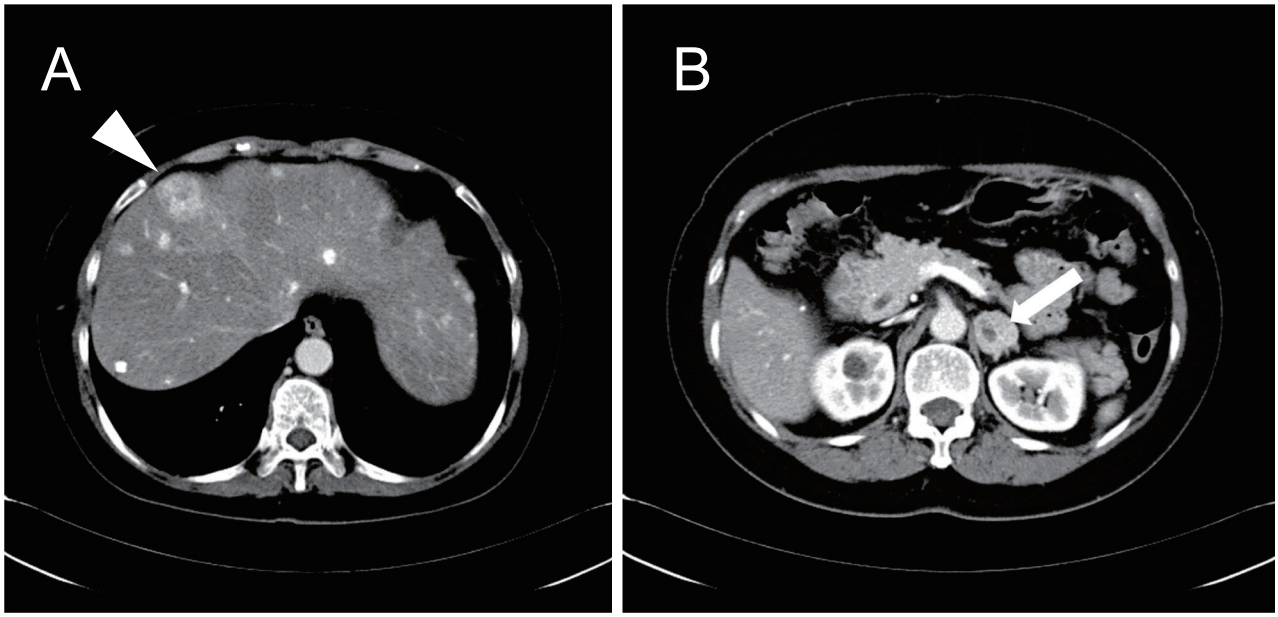

Fig. 3 Contrasted computed tomography of the abdomen. The white arrowhead indicates liver metastasis of medullary thyroid carcinoma (A). The white arrow indicates a left adrenal tumor (B).

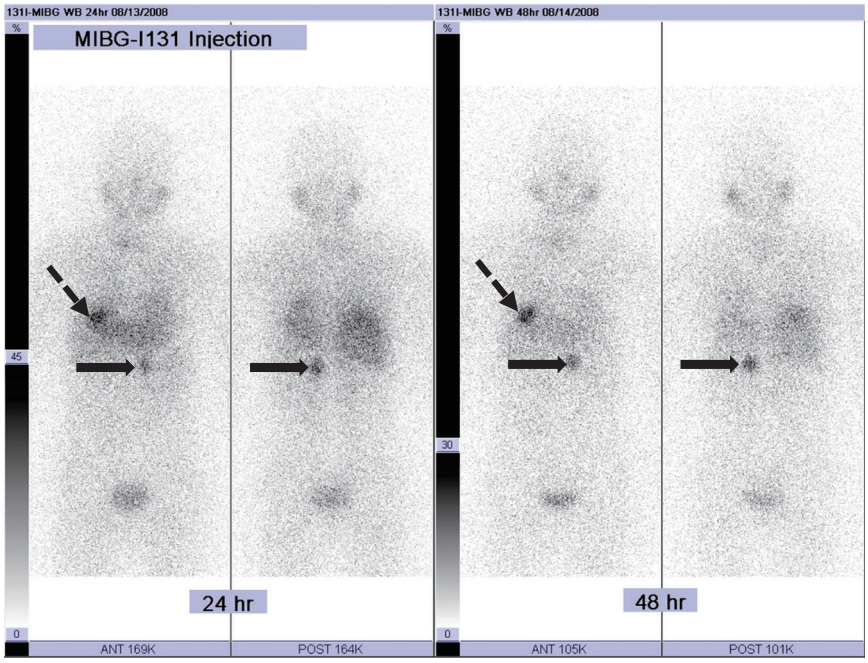

Fig. 4 Iodine 131-labeled metaiodobenzylguanidine scintigraphy shows involvement of the left adrenal gland and the liver. Black arrows indicate the left adrenal tumor, and black broken arrows indicate the liver tumor. These findings suggest PCC of the left adrenal gland and liver metastasis of MTC.

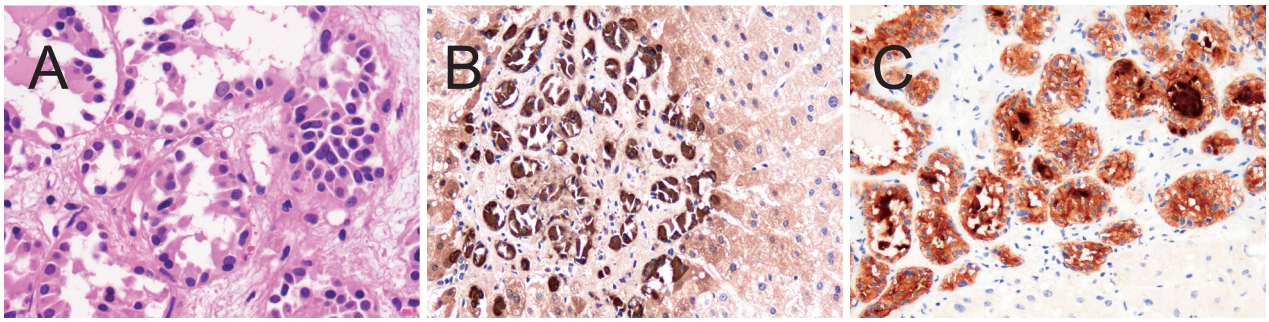

Fig. 5 Hematoxylin and eosin staining of a liver needle biopsy specimen showing characteristic features of sheets and trabecular, polygonal, round, or spindle cells, separated by a fibrovascular stroma (Fig. 5A). The cells show expression of carcinoembryonic antigen (Fig. 5B), and calcitonin (Fig. 5C).

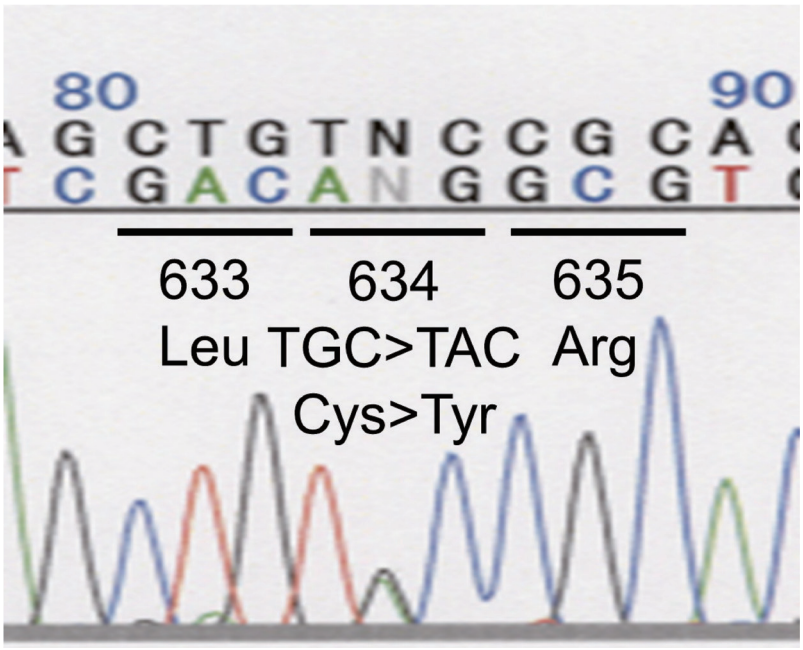

Fig. 6 Genetic analysis shows a heterozygous point mutation of the RET gene, TGC to TAC at codon 634, resulting in the substitution of cytosine with leucine (C634Y).

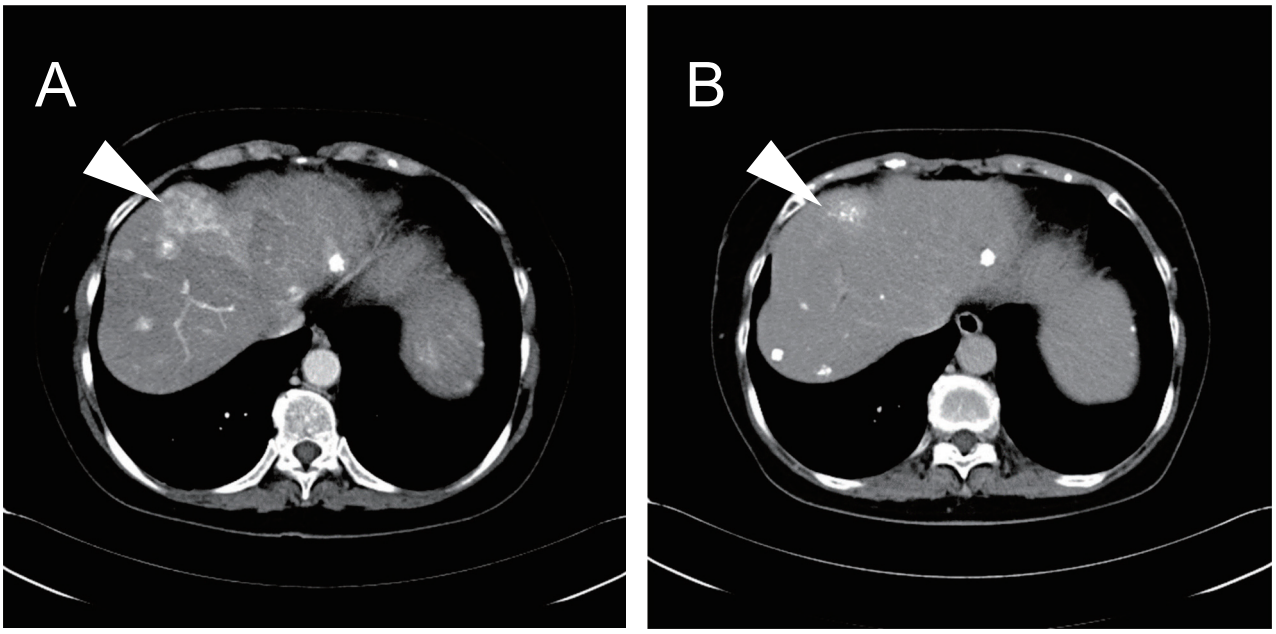

Fig. 7 After 7 years of conservative observation, the maximum diameter of the MTC metastasis of the liver increased to 52 mm, indicated by the white arrowhead (Fig. 7A). After treatment, the maximum diameter of 52 mm decreased to 36 mm, as illustrated by the white arrowhead (Fig. 7B).

These features confirmed the MTC liver metastasis.

The left adrenal tumor was laparoscopically removed, and the pathological findings confirmed PCC. The MTC was not surgically removed because of the liver metastasis. The status of the MTC was compatible with that of T1N1M1 and stage IVC.

After providing written informed consent, the patient, the patient's son and two daughters underwent RET gene analysis. The investigation was conducted in accordance with the principles of the Declaration of Helsinki and the study was approved by the Institutional Review Board Committee at Tokai University School of Medicine. Genetic analysis using the standard protocol [9, 10], revealed a heterozygous point mutation of the RET gene, TGC to TAC at codon 634, resulting in the substitution of cytosine with leucine (C634Y) (Fig. 6). The patient's son and two daughters had the wild-type RET gene.

After 7 years conservative observation, the maximum diameter of the MTC liver metastasis increased to 52 mm on contrasted CT scan (Fig. 7A) and lenvatinib was available in Japan. Lenvatinib was administered at an initial dosage of 24 mg once a day. The response was objectively evaluated by medical imaging findings and the Response Evaluation Criteria in Solid Tumours (RECIST) guideline (version 1.1) [11]. Adverse events (AEs) of lenvatinib were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [12].

The lenvatinib dosage of 24 mg once a day was continued for 35 days. The patient complained of nausea and appetite loss but no body-weight loss and dehydration were observed. Therefore, her nausea was evaluated as grade 2 based on CTCAE. The dosage of lenvatinib was gradually decreased to 20 mg once a day for 15 days, and 14 mg once a day for 14 days, because of the nausea. Eventually, we discontinued administration of lenvatinib because the patient was unable to tolerate the nausea. After administration of a total dose of 1336 mg lenvatinib, the effect was evaluated by contrasted CT scan. The maximum diameter of the tumor had decreased to 36 mm (Fig. 7B), and reduction of 31%, which we evaluated as partial response (PR). The patient was doing well 2 years later and conservatively observed at the outpatient clinic.

DISCUSSION

We described a 61-year-old Japanese female with MTC, liver metastasis of the MTC, and PCC of the left adrenal gland. The patient was diagnosed with MEN2A caused by C634Y mutation in the RET gene. It was proposed that the patient had no PHP, because serum calcium and intact PTH levels were within normal ranges and parathyroid adenoma and hyperplasia were not observed on ultrasonography. PHP reportedly occurs in approximately 30% of patients with MEN2A caused by RET 634 mutations [4]. Then, it was indicated that PHP was not observed in our patient.

The father of the patient had medical history of thyroidectomy for the thyroid tumor and abdominal surgery to remove the abdominal tumor. Altough the pathological findings were unclear, the family history suggested that the C634Y mutation in the RET gene was inherited from the father.

C634Y mutation in the RET gene is considered to pose high risk of aggressive MTC, according to revised American Thyroid Association guidelines for the management of MTC [13]. The patient's son and two daughters had wild-type RET gene. If they had RET mutation of C634Y from the mother, prophylactic surgery of the thyroid may be recommended [1].

The PCC was laparoscopically removed, because hypertension caused by PCC should be avoided. But thyroidectomy for the MTC was not performed because of the liver metastasis. The only treatment for MTC is surgery, but the timing of surgery is crucial in MEN2A. Ideally, true prophylactic thyroidectomy or early thyroidectomy should be performed in patient

with RET gene mutation that is clinically asymptomatic before the development of MTC or at least when the MTC is confined to the thyroid and before the disease spreads beyond the thyroid [1]. Because our patient had MTC with the liver metastasis at the first visit, it was proposed that surgery would not be curative [1]. Therefore, we had to conservatively observe the patient for 7 years.

It has been suggested that TKIs offer new treatment options for pateints similar to ours [4]. Lenvatinib, a TKI, has been reported to have objective response rate (ORR) of 36% and median time to response (TTR) of 3.5 months by RECIST [14], and the RET gene status did not correlate with the treatment outcomes [14]. It has been concluded that lenvatinib has high ORR and short TTR in patients with advanced MTC. Our patient showed PR after 135 days of lenvatinib administration. The outcome of this study was consistent with that of the previous report [14]. If lenvatinib were available, lenvatinib should be administered at the first visit. Lenvatinib might be more effective on the patient 7 years ago.

All patients experience AEs, with the most common toxicity criteria grade 3 or 4 of AEs, being diarrhea (14%), hypertension (7%), decreased appetite (7%), fatigue, dysphagia, and increased alanine aminotransferase levels (5% each, respectively) [14]. Because the patient experienced grade 2 nausea, she was reluctant to take lenvatinib after receiving a total dose of 1336 mg. But our patient showed PR in MTC liver metastasis, indicating that lenvatinib had effectively treated liver metastasis of the MTC.

Tyrosine kinase receptors, RET, VEGFR, FGFR, PDGFR, and KIT, for angiogenic factors represent putative targets for pharmacotherapeutic intervention of tyrosine kinase inhibitor in carcinoma. It was reported that antiangiogenic activity of lenvatinib correlated with antitumor activity in patients with a wide range of solid malignant tumors, colon carcinoma, non-small cell lung carcinoma, renal carcinoma, gastric carcinoma, pancreatic carcinoma, ovarian carcinoma, esophageal carcinoma, endometrial carcinoma, breast carcinoma, and sarcoma [15, 16]. In Japan, lenvatinib is clinically used for the treatment of unresectable hepatocellular carcinoma [17].

In conclusion, lenvatinib showed PR in a patient with liver metastasis of MTC caused by MEN2A with C634Y mutation. This implies that lenvatinib can be the treatment of choice against advanced MTC.

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AUTHOR CONTRIBUTIONS

H Sato is a consultant endocrinologist. Y Saito and Y Suzuki are breast and endocrine surgeons. C Inomoto is a pathologist. H Sato, Y Saito, and Y Suzuki contributed equally to the management of this patient and the drafting of the report. C Inomoto contributed to the pathological diagnosis and drafting of the report. H Sato is a corresponding author. H Sato has moved to Kanagawa Dental University from Tokai University School of Medicine.

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